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The studies are based on assessment of inorganic phosphate and its modulation of oxygen transport by virtue of its effect on the production of glycolytic intermediates, primarily 2-3 diphosphoglycerate and adenosine triphosphate. The interaction of these systems with the red cell results in modulation of the oxyhemoglobin dissociation curve and, by inference, oxygen delivery to tissue. The studies herein reported establish the very significant feature of the con-→

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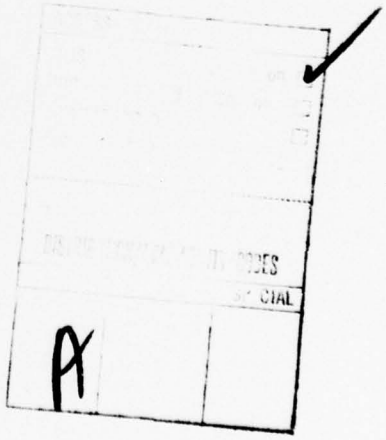
20. tinued dissection of the Fick equation in that we have demonstrated that tissue oxygen tension is the best predictor of systemic oxygen transport. Systemic oxygen transport (STO_2) is the measure by which blood flow, hemoglobin, P50 of the oxyhemoglobin curve, are combined in total assessment of oxygen delivery. Establishment of the correlation between systemic oxygen transport and tissue oxygen tension has significance for the totality of oxygen transport as well as suggesting that tissue oxygen tension may have important use as a minimally invasive monitor in many situations of critical illness. It also has the advantage of being readily available and capable of being used in unusual systems of transport of victims.

The second aspect of this year's work has been the correlation of nitrogen balance, an indicator of catabolic illness in patients with injury, with red cell 2-3 DPG levels. The significance of this is the further delineation of the red cell as a biological biopsy of ready availability in situations following injury. The correlation between red cell glycolysis and nitrogen balance suggests a reflection in a unique cell, the red cell, of total body response to injury and massive transfusion.



THE ROLE OF INORGANIC PHOSPHATE IN OXYGEN TRANSPORT

ANNUAL PROGRESS REPORT

George F. Sheldon, M.D.

February 28, 1976

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The two features of the proposal which began this contract in 1971 were an analysis of the effect of transfusing blood of extended storage life with diminished levels of 2,3 diphosoglycerate and increased affinity for oxygen and the role of inorganic phosphate during recovery from transfusion. We projected a series of acute studies in which all components of the Fick equation were analyzed. The Fick equation dissection was done by measuring cardiac output, arterial and venous blood gases and saturations, P_{50} of the oxyhemoglobin dissociation curve, 2,3 diphosphoglycerate, adenosine triphosphate, serum inorganic phosphate levels, and tissue oxygen tension. As indicated in the last Annual Report, an extensive statistical analysis was begun to determine cause, effect and military significance of the hemodynamic changes seen in these particular studies. The theorem initially advanced was than an acute, left shift in the oxyhemoglobin dissociation curve would parallel an increase in cardiac output to prevent tissue hypoxia. We reasoned that normalization of the oxyhemoglobin curve occurred by mobilization of serum inorganic phosphate which enhanced red cell glycolysis, by acting as a cofactor at the glyceraldehyde -3-phosphate-dehydrogenase step of the Emden-Myerhof pathway. By monitoring the oxyhemoglobin curve's return to normal, information could be obtained about demand mechanisms and potential deleterious effects of transfusing acutely injured patients with blood of extended shelf life (which is considered adequate by current blood banking regulations).

The assessment of the effect of relatively small changes in the P_{50} of the oxyhemoglobin dissociation curve has been hampered by the lack of physiological models which are independent of autoregulatory mechanisms and factors such as temperature and pH which are known to affect the oxyhemoglobin dissociation curve. Effects of altered oxyhemoglobin dissociation on diverse organ systems and levels of oxygen transport, particularly at tissue level, have been difficult to assess. Changes in components such as oxygen extraction could be minimized by compensatory changes in blood flow. Previous reports have not adequately assessed the effects of transfusing stored blood because all components of oxygen transport were not individually measured and analyzed.

This report deals with data obtained from seven patients admitted to the Intensive Care Unit. A criterion for inclusion in the study was that the patient required arterial and pulmonary artery catherization as part of his care and NOT as a requirement of the protocol. All patients received stored blood greater than 20% of their estimated blood volume on the day of sampling. Simultaneous samples for determination of arterial and mixed venous blood gases and saturations were performed.

Measurements of hemoglobin, cardiac output, whole blood lactic acid, P_{50} of the oxyhemoglobin dissociation curve, red cell 2,3 diphosphoglycerate, adenosine triphosphate, and, in the sample reported here, subcutaneous tissue oxygen tension were analyzed. Rectal temperature and arterial and venous pressures were measured, also. The first sampling period took place immediately after transfusion was complete. Samples were repeated at 4 to 6-hour intervals.

Blood gas analysis was performed in duplicate on Instrumentation Laboratory and Radiometer blood gas analyzers. Hemoglobin saturation levels were measured spectrophotometrically on the Instrumentation Laboratory 182 Co-oximeter. Cardiac outputs were performed in triplicate by indicator dilution, using indocyanine green dye in five patients, and with thermodilution in two patients. Lactic acid was measured using a Boehringer kit and expressed as millimoles per liter whole blood. Red cell 2,3 DPG was measured using the Sigma kit, and adenosine triphosphate by the Calbiochem kit, and values expressed in micromoles-gm Hb. The oxyhemoglobin dissociation curves (P_{50}) were derived from saturation and pH measurements after equilibration of blood with three Scholander-analyzed gas mixtures containing oxygen with partial pressures between 15 and 60 millimeters of mercury with PCO_2 of 40 mm/Hg. Corresponding P_{02} values were corrected to normal conditions of pH=7.4, using the formula $\Delta \log P_{02} = -0.40 \Delta pH$. After saturation was measured the Hill equation was used to derive the P_{50}. The resultant P_{50} values under standard conditions of $PCO_2 = 40$, temperature =37°C. were employed in the analysis to differentiate the P_{50} variation due to storage from that due to the Bohr effect and temperature.

Subcutaneous tissue oxygen tensions (PTO_2) were measured by the method of Hunt. (1) Normal saline was pumped through subcutaneously implanted silicone rubber tubing (o.64 mm I.D. x 1.19 mm O.D. x 10 centimeters) at a rate of 2.5 ml. hour. This rate was slow enough to permit a 95% equilibration of oxygen. The tubing effluent was aspirated anaerobically and its P_{02} measured with a Clark electrode. Because PTO_2 declines in normal subjects as a function of duration of implantation the results were expressed as a percent of the normal value for the day of sampling. All tissue oxygen tensions were obtained after the tube had been in place at least 24 hours to allow stabilization.

A scale for the magnitude of storage effect was provided by expressing the volume of transfusion as a fraction of the patient's estimated blood volume and multiplying this number by the mean storage time in bank days of transfusion units. Arterial and venous oxygen contents were calculated from the

formula: O_2 (ml/dl) = 0.003 PO_2 + (1.39 x Hb X proportional saturation). Because the experimental design required simultaneous measurement of all components, statistical analysis was performed on complete sets of data only. Multiple linear regressions were done using a stepwise backward elimination technique. (2) Values were transformed as necessary to comply with the assumptions of the statistical model. Variables were eliminated from analysis if their correlation coefficients indicated that they played no significant role in the systems under investigation, and subsequently if their partial regression coefficients were not significant at the 10% level, or if their elimination did not entail a significant increase in the mean square due to deviations. Means are reported plus or minus one standard deviation, or, when transformations were required, with the sample range.

RESULTS

Patient Population

Table 1 gives correlation coefficients and mean values for the variables retained in the analyses. Red cell function was moderately depressed (P_{50} = 25.0, range 19.7 - 28.3) with a mean storage time of only 2.6 days and a mean transfusion volume of 40% estimated blood volume. Although cardiac index (mean 3.94$\pm$ 1.39) is within "normal" limits, the extraction parameters suggest a moderate oxygen debt for the group as a whole (lactate = 2.83, range 1.17-18.60; S_vO_2 = 65.0 $\pm$ 11.9; P_vO_2 = 33.33 $\pm$ 8.0). Mean arterial oxygen tension was 99 mm.Hg (range 40-495).

Mean rectal temperature was 38.1 $\pm$ 1.0. Temperature correlated significantly with total peripheral resistance ($r = -0.47$, $p<.05$), DPG ($r = .40$, $p<.05$), and S_vO_2 ($r = -0.50$, $p<.05$). It did not correlate with P_{50}, cardiac output, or PTO_2, and was not retained in the analyses of these variables. Hemoglobin ranged from 8.7 to 17.4 (mean = 11.23) and was not significantly associated with any variable. Percent blood volume administered was positively correlated with mean storage time (MST). Arterial oxygen tension was positively correlated with cardiac index, but not when P_{50} was held constant mathematically (partial $r = 0.24$, n.s.). ATP was correlated with DPG ($r = 0.59$, $p<.005$) and with MST ($r = -0.44$, $p<.05$), but not with P_{50}.

Determinants of P_{50}

Mean storage time was the single most important factor influencing P_{50}. Taken alone, it accounted statistically for 47.5% of the variation in P_{50} ($R^2 = 0.475$), with another 13% attributable to 2,3 DPG and pH effects during the immediate recovery period. Part of the P_{50}/2,3 DPG relationship best represents in vivo restoration of red cell glycolytic intermediates, as evidenced by the significant correlations between 2,3 DPG and pH and S_vO_2. The additional contribution of pH may be a trivial effect of the Bohr shift correction. P_{50} declined an estimated 0.3 mm Hg per day in storage.

Assessment of Oxygen Delivery in the Periphery

A comprehensive quantitation of the physiologic significance of depressed P_{50} has awaited a means of measuring tissue oxygen tension (PTO_2). In a related study we found that PTO_2 provided an extremely sensitive, real-time indicator of systemic oxygen transport (STO_2, or the product of cardiac index and arterial oxygen tension) (3). Lactic acid production, while dependent on oxygen flow, reflects primarily anaerobic metabolism in muscle. PTO_2 measures the delivery of oxygen in subcutaneous tissue and represents an additional potential for differentiation of the various elements of oxygen transport. As reported in previous studies from our laboratory, it reflects changes in perfusion-oxygenation relationships before blood pH and PO_2 become abnormal (Fig. 1), and it provides a better measurement of oxygen debt than lactate does in subjects where the latter is elevated (4).

In our transfused patients fifty-two percent of systemic oxygen transport was accounted for by tissue oxygen tension (PTO_2). When the effect of P_{50} on tissue oxygenation was statistically analyzed an unexpected result was found. The acute change in oxygen affinity seen after transfusion resulted in an increase in tissue oxygen tension (Fig. 1). This seeming paradox is explained by elevated cardiac output, which was the compensatory mechanism determined to be most important in maintenance of tissue oxygen tension. Low P_{50} values following transfusion were also associated with changes in S_vO_2, P_vO_2, total peripheral resistance and arterial pressure which paralleled the changes in PTO_2 (Table 1).

P_{50} and Cardiac Output

We postulated that the high cardiac output found in patients recovering from massive transfusion was in part compensation for a left-shifted oxyhemoglobin dissociation curve. When the Fick equation is mathematically modelled, a three-fold cardiac output increase at a constant AVO_2 would theoretically be required to accommodate a P_{50} of 18, which is frequently present after massive transfusion. It is also postulated that oxygen extraction, reflected in lowering of S_vO_2, would compensate in part for the left shift of the oxyhemoglobin dissociation curve. Our data at present indicate that a significant correllation ($r=-.55, p<.005$) occurs between a left shifted post-transfusion oxyhemoglobin dissociation curve and cardiac index following transfusion. If, however, cardiac output cannot rise to compensate for decreased P_{50}, and lactic acidosis ensues, then this relationship ceases to exist (Fig. 2). In patients without lactic acidosis, then, increased affinity of hemoglobin for oxygen can require an increase in cardiac output, reflected in the periphery as an increase in PTO_2. In patients with elevated lactate, however, the flow-demand relationship is primary.

Discussion

Increased affinity of hemoglobin for oxygen should require an increase in cardiac output to maintain a given level of oxygen delivery. Recent studies support this hypothesis, but without specifying a physiological mechanism through which the increased flow is initiated (5,6,7). In the intact animal chemoreceptors do not influence cardiac output until PAO_2 is less than 60. Evidence of anaerobic metobolism in the form of lactate production does not appear until arterial oxygen tension has fallen to less than 36 mm.Hg (8).

If cardiac output does not compensate for increased hemoglobin oxygen affinity, then other elements of oxygen uptake should reflect the putative deficit in oxygen unloading occasioned by receiving high affinity hemoglobin blood transfusion. Riggs in baboons has recently shown a decrease in venous oxygen tension with increased oxyhemoglobin affinity and no significant changes in other components of oxygen transport (9). In a hind limb preparation Yhap showed a diminished arterial venous oxygen difference with acute decreases in the P_{50} of the oxyhemoglobin dissociation curve (10). Both authors felt that the changes they have observed have little clinical significance except in situations when oxygen tension is approaching a critical level for cellular metabolism.

Other studies reporting oxygen transport effects of banked blood are interpreted with difficulty because the authors express P_{50} values at the temperature, PCO_2, and pH of the subjects blood. The normalised P_{50}, of course, is a fairly artificial expression, but converting standard P_{50} values to physiological conditions makes assigning a causal role to oxyhemoglobin dissociation more problematical. Variations in P_{50} then become a partial function of the behavior of the system they are supposed to affect. In addition, the multiplicity of points at which a P_{50} effect can be expected - changes in flow, central blood gas tensions and saturations, and peripherally based measurements such as lactate - makes estimating the net magnitude of the effect exceedingly difficult. Small simultaneous changes in all parameters may escape statistical notice yet have a considerable over all impact. The primary nature of the P_{50}-$\dot{Q}$ relationship was important to us in this respect.

A possible mechanism by which P50 may influence flow has recently come to light. Duling has shown that microvascular tone is influenced by changes in ambient PO_2 in the same range as our PTO_2 values (11). With rising oxygen tensions, precapillary sphincters become more constricted. Thus decreasing affinity of hemoglobin for oxygen at the precapillary level might lead to a net constriction of the microvasculature and reduction in flow. Because oxygen delivery is largely flow-determined, as reflected in the correlations between lactate, PTO_2 and cardiac index, the net effect of rising P_{50}'s with decreasing cardiac output is reflected by falling $P_{\bar{v}}O_2$'s and PTO_2's and rising lactate. The stress condition of injured transfused subjects on the whole and establishing P_{50} as a truly independent variable makes it possible to specify the massive transfusion effect. Because arterial oxygen tension is not depressed to a point where central chemoreflectors are activated and because of the low tissue oxygen tension, we conclude that local effect on microvascular tone is a likely mediator of the cardiac response to increased affinity of hemoglobin for oxygen.

Red Cell Function, Inorganic Phosphate and Nutritional Status

These studies suggest that the red cell reflects the total body's energy interaction. Red cell diphosphoglycerate values correllate positively with the quantity of protein administered as well as with total daily calories.

DPG: Protein mg/Kg/day $r=0.634, p<.001$
DPG: Nitrogen balance mg/Kg/day $r=0.674, p<0.001$
DPG: Calories/Kg/day $r=0.721, p<0.001$
Protein Nitrogen: P_I $r=0.56, p<0.05$

These findings suggest that nitrogen incorporation is associated with positive phosphate balance and that red cell glycolysis reflects that association. Our prior work relating phosphate needs to non-protein calories received is extended to include nitrogen repletion. Rudman's work, relating protein repletion to elemental balance would support that observation (12).

TABLE 1

Correlations

	2,3 DPG	pHa	Mean Storage Time	TPR	MAP	Lactate	Tissue O_2	A-VO_2	P_vO_2	S_vO_2	$\dot{Q}$
P_{50}	.688***	.473*	-.689***	.290	-.285	.342	-.466*	.443*	-.511**	-.503**	-.550**
2,3 DPG		.423*	-.641***	.043	-.135	.349	-.335	.418*	-.504**	-.610***	-.401*
pHa			-.198	.411*	-.003	-.042	-.131	-.040	-.534**	-.008	-.389*
Mean Stg Time				.021	.476*	-.530**	.312	-.424*	.296	.462*	.359
TPR					-.018	.134	-.507**	.115	-.316	-.003	-.708**
MAP						-.709***	.542**	-.325*	.366**	.260*	.491***
Lactate							-.670***	.438*	-.484**	-.474**	-.644***
Tissue O_2								-.200	.484*	.369***	.783***
A-VO_2									-.461*	-.744***	-.669***
P_vO_2										.693***	.620*
S_vO_2											.435

* $p < .05$ ** $p < .01$ *** $p < .001$

Mean Values

Variable	P_{50}	2,3 DPG	pHa	Mean Storage Time	TPR	MAP	Lactate	P_TO_2	A-VO_2	P_vO_2	S_vO_2	$\dot{Q}$
Expression	mm Hg	M/gHb-1		da	dynes-sec/cm^5/m^2	mm.Hg	M/l whole blood	percent normal	ml/dl	mm Hg	percent	l/min/m^2
Arith. Mean	24.91	14.52	7.460	3.225	643.6	94.9	4.569	89.3	5.108	33.3	65.03	3.941
Mean from Transformed Values	25.04	14.11	-	2.575	-	-	2.829	76.6	-	-	-	-
±S.D. or (range)	(19.7-28.3)	(9.6-23.3	±0.008	(0.88-10.13	±253.4	±18.6	(1.17-18.60)	(22-218)	±1.561	±8.0	+11.94	±1.387

FOOT NOTES

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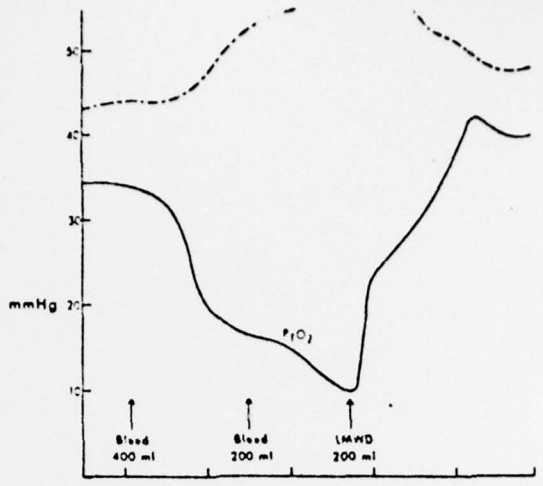
LEGEND for TABLES and ILLUSTRATIONS

TABLE 1. Correllation coefficients among the many variables examined in the recovery from massive transfusion. Statistical analysis of this nature allows quantitation of oxygen transport and makes possible assessing the significance of different variables.

FIGURE 1. The illustration (top) is from related studies in dogs with hemorrhagic shock and is reproduced for contrast (4). Hemorrhagic shock is associated with low values of tissue oxygen (PTO_2). By contrast, when resuscitation is successful, cardiac output elevates (bottom) with elevated PTO_2 even in the setting of massive transfusion and low P_{50} values of the oxyhemoglobin dissociation curves.

FIGURE 2. Significant estimators of oxygen transport. The histograms depict the amount of variation in systemic oxygen transport (STO_2) which can be accounted for by the variables listed, i.e. lactate, tissue oxygen (PTO_2), and central venous oxygen tension (S_vO_2). In the large histogram (left) lactic acidosis was present and tissue oxygen was the measurement which most accurately reflected oxygen transport. In non-acidotic subjects no single variable correllated well with systemic oxygen transport.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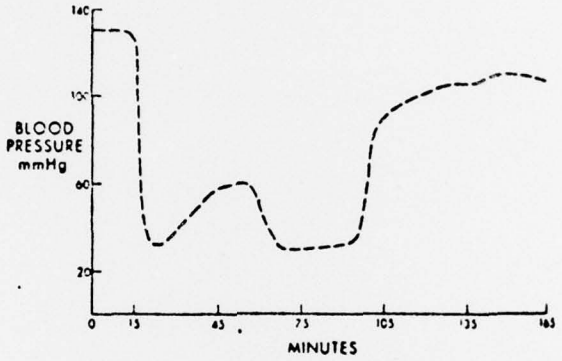
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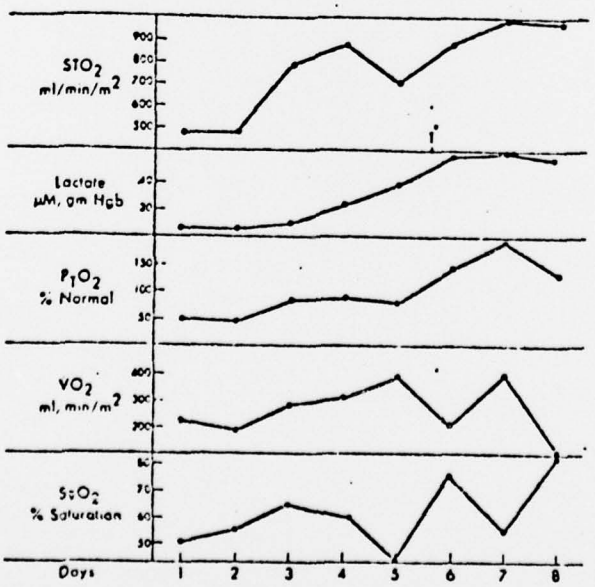
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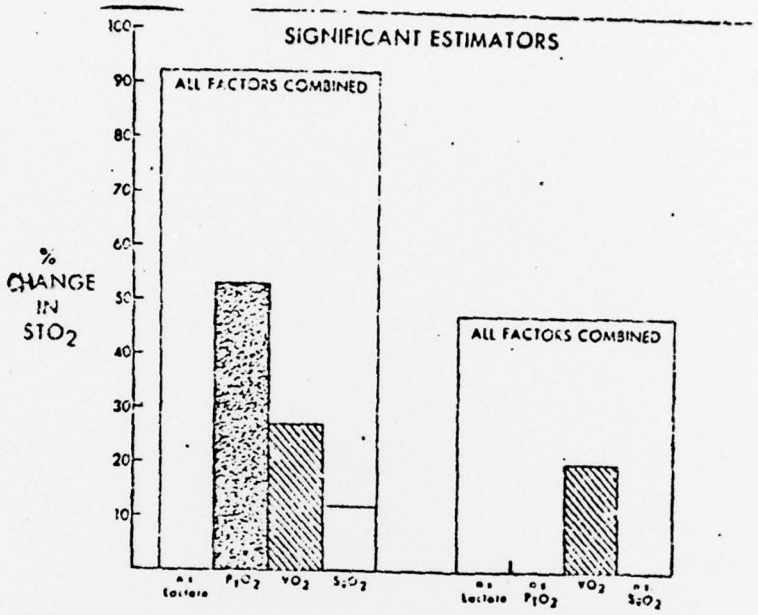
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Fig. 2

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